

Applicant: A. Smith, et al.  
Application No.: Unassigned  
Filing Date: Herewith  
Docket No.: 903-194 PCT/US  
Page 2

**A. Amendments to the Specification:**

Please add the following immediately after the title of the invention:

**CROSS-REFERENCE TO RELATED APPLICATIONS:**

This application is the National Stage of International Application No. PCT/NL2004/000018, filed January 9, 2004, the contents of which is incorporated by reference herein.

Please add the following new paragraph immediately prior to page 1, line 1, and after the Cross Reference to Related Applications, as follows:

**FIELD OF THE INVENTION:**

Please add the following new paragraph immediately prior to page 1, line 5, as follows:

**BACKGROUND OF THE INVENTION:**

Please add the following new paragraph immediately prior to page 1, line 32, as follows:

**SUMMARY OF THE INVENTION:**

Please amend the paragraph beginning at page 1, line 32, as follows:

The present inventors have now found a novel method for the catalytic reduction of amides for the preparation of amines at mild reaction conditions to obviate the above drawbacks, i.e. at a temperature of below 200°C and a pressure of below 50 bar, by performing the said reduction reaction at the above mild reaction conditions with numerous bimetallic and trimetallic catalysts. ~~Said experiments were performed by high-~~

Applicant: A. Smith, et al.  
Application No.: Unassigned  
Filing Date: Herewith  
Docket No.: 903-194 PCT/US  
Page 3

~~throughput experimentation, as e.g. is described in EP 1001846. It was found that a catalyst, chosen from bimetallic and trimetallic catalysts of the group, consisting of ABC, AB, AC and BC, wherein:~~

~~A is a metal, chosen from the group, consisting of Co, Fe, Ir, Pt, Rh and Ru,~~

~~B is a metal, chosen from the group, consisting of Cr, Mo, Re and V, and,~~

~~C is a metal, chosen from the group, consisting of Cu, In and Zn, were~~

~~surprisingly suitable for the reduction of amides at mild reaction conditions.~~

Please delete the paragraphs from page 2, line 14, to page 6, line 11.

Please add the following new paragraph immediately prior to page 6, line 12, as follows:

BRIEF DESCRIPTION OF THE DRAWINGS:

Please add the following new paragraph immediately prior to page 7, line 2, as follows:

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS:

Please add the following new paragraphs at page 7, line 3 and after the "DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS:", as follows:

Said experiments were performed by high-throughput experimentation, as e.g. is described in EP 1001846. It was found that a catalyst, chosen from bimetallic and trimetallic catalysts of the group, consisting of ABC, AB, AC and BC, wherein:

A is a metal, chosen from the group, consisting of Co, Fe, Ir, Pt, Rh and Ru,

B is a metal, chosen from the group, consisting of Cr, Mo, Re and V, and,

C is a metal, chosen from the group, consisting of Cu, In and Zn, were surprisingly suitable for the reduction of amides at mild reaction conditions.

The reduction process is preferably performed with a heterogeneous catalyst. However, it is not necessary for the metals of the catalyst to be bound on the same support. E.g., one of the metals can be present on a carbon support, whereas another metal of the said catalyst can be present on e.g. a silica, titania or carbon support. The skilled person is aware of suitable supports for the envisaged catalysts. It is also possible to provide a metal of the catalyst on different supports. It is however preferred to provide the bimetallic and/or trimetallic catalyst on similar support material, although the different metals do not necessary have to be present on the very same support particles.

Preferably, the support is chosen from carbon, titania, amorphous silica-alumina and silica or a combination thereof.

It has been found that, using the catalysts as identified above, the catalytic reduction can even be performed at pressures of 30 bar or less, even at 15 bar or less. As will be explained below, the method according to the invention can also successfully be performed at a pressure of 10 bar, preferably between 5-10 bar, more preferably between 6-10 bar.

In a preferred embodiment, the reduction is performed in a continuous flow mode. Although according to the invention such a continuous flow mode can be performed in a liquid phase, it is preferably performed in gaseous phase, i.e. wherein one or more, preferably all of the reactants are passed in gaseous phase over the catalyst at the above-mentioned reaction conditions.

It is also been found that the above method according to the invention can successfully be performed at a temperature of 160°C or less, even at a temperature of 130°C or less. Also, it has been found that the method can be suitably performed at a temperature between 70-100°C, preferably around 80°C. "About" means that a deviation of 5°C is allowed.

However, in another preferred embodiment, the method of the invention is performed at batch mode reactions, e.g. wherein at least one but preferably all of the reactants are in a liquid phase, e.g. in solution, and contacted with the catalyst. At batch mode reaction conditions, the

Applicant: A. Smith, et al.  
Application No.: Unassigned  
Filing Date: Herewith  
Docket No.: 903-194 PCT/US  
Page 5

amide substrate is dissolved in an appropriate solvent, such as an acid, an ether, an ester or an alcohol, preferably an acid, preferably a Bronsted acid, more preferably an organic acid. The term "Bronsted acid" is well known in the art. Carboxylic acid is a preferred organic acid; most preferably, the organic acid comprises acetic acid. The solvent preferably has a pKa value of 5 or less, more preferably between 3 and 5. The preferred concentration of the acid, preferably organic acid, more preferably carboxylic acid and most preferably acetic acid is up to 1.0 M, preferably between 0.2 and 0.8 M, more preferably between 0.4 and 0.5 M. An internal standard, such as n-decane can be co-added to the reaction mixture for quantitative gas-chromatography analysis.

In batch mode reactions according to the invention, the addition of an additive may be favoured. The additive preferably comprises an acid, more preferably a Lewis acid, most preferably a boron-containing compound. The term "Lewis acid" is well known in the art. The substrate:additive ratio in the reaction mixture is preferably 4 or less, more preferably 2 or less, and most preferably between 0.9-1.1. During the reaction, the reaction mixture is preferably subjected to hydrogen pressures between 1 and 17 bar, more preferably between 5 and 10 bar. The reaction temperature is preferably between 90 and 140°C, more preferably between 100 and 130°C.

According to a preferred embodiment of the method of the invention, both for flow and batch mode reactions, the catalyst is chosen from the group, consisting of:

CoCu	IrMoCu
FeIn	IrReCu
FeRe	IrReZn
IrMo	IrVZn
IrRe	PtMoCu
IrV	PtMoIn
MoIn	PtMoZn
PtMo	PtReCu
PtRe	PtReIn
PtV	PtReZn
ReIn	PtVIn

Applicant: A. Smith, et al.  
Application No.: Unassigned  
Filing Date: Herewith  
Docket No.: 903-194 PCT/US  
Page 6

RhCu	PtVZn
RhIn	RhMoCu
RhMo	RhMoIn
RhRe	RhMoZn
RhV	RhReCu
RuRe	RhReIn
CoMoZn	RhReZn
CoReCu	RhMoZn
CoReIn	RhVIn
CoVIn	RuReCu
FeCrIn	RuReZn
FeReCu	
FeReIn	
FeReZn	

Preferably, the catalyst is chosen from the group consisting of PtRe, IrMo, IrRe, PtRe, PtV, RhRe, RhV, FeReIn, PtReCu, PtReIn, PtReZn, RhMoCu, RuReZn, PtMo, RhMo, RuRe, IrReZn and PtMoCu, most preferably more preferably from the group consisting of PtRe, PtReCu, PtReIn, FeReIn, PtMo, PtV, RhMo, PtMoCu, RhMoCu, and RuRe, even more preferably from the group, consisting of PtReCu, PtReIn, FeReIn, PtMo, PtV, RhMo, PtMoCu, RhMoCu, PtRe and RuRe, and most preferably from the group consisting of PtReCu, PtRe, PtMo, IrReZn, PtMoCu and PtReIn. As will be shown in the Examples, the above-identified catalysts can effectively be used at the mild reaction conditions according to the invention.

In a further aspect, the invention relates to novel bi- or trimetallic catalysts for the reduction of amides to amines, chosen from the group, consisting of:

CoCu	IrMoCu
FeIn	IrReCu
FeRe	IrReZn
IrMo	IrVZn
IrRe	PtMoCu
IrV	PtMoIn
MoIn	PtMoZn
PtMo	PtReCu
PtRe	PtReIn
PtV	PtReZn

ReIn	PtVIn
RhCu	PtVZn
RhIn	RhMoCu
RhV	RhMoIn
CoMoZn	RhMoZn
CoReCu	RhReCu
CoReIn	RhReIn
CoVIn	RhReZn
FeCrIn	RhMoZn
FeReCu	RhVIn
FeReIn	RuReCu
FeReZn	RuReZn

more preferably from the group, consisting of IrMo, IrRe, PtRe, PtV, RhV, FeReIn, PtReCu, PtReIn, PtReZn, RhMoCu, RuReZn, PtMo, IrReZn and PtMoCu, preferably chosen from the group, consisting of FeReIn, PtReCu, IrReZn, PtMoCu, PtRe and PtReIn, and most preferably chosen from the group, consisting of PtReCu, PtRe, PtMo, IrReZn, PtMoCu and PtReIn.

The catalyst is preferably supported on a carrier, as outlined above.

In a further aspect, the invention relates to a method for the selection of at least one bi- or trimetallic catalyst, active in the reduction of amides into amines from a collection of bi- and/or trimetallic catalysts, comprising the steps of

- A) preparing the catalysts on separate carriers,
- B) loading the catalysts prepared in step A) in separate reactor vessels, the vessels having a parallel arrangement,
- C) feeding and incubating the reactor vessels with an amide and hydrogen at identical conditions regarding at least one of the quantities, chosen from reaction time, temperature and pressure,
- D) measuring the conversion of amides into amines in each reactor vessel,
- E) selecting one or more of the catalysts, based on the measured conversion in step D).

This method allows the rapid identification and selection of active catalysts for the reduction of amides; a large range of different catalysts, having a different metal composition or

Applicant: A. Smith, et al.  
Application No.: Unassigned  
Filing Date: Herewith  
Docket No.: 903-194 PCT/US  
Page 8

ratio between the metals can be tested in the hydrogenation reaction, wherein the reaction conditions can be controlled and optimised. Thereto, the different catalysts are prepared on separate carriers, according to methods, known in the art. Preferably, in step A) the catalysts are prepared in parallel. The carriers can be the same for the catalysts to be tested, but may also be different in order to test and select an optimal catalyst-carrier combination. Then the prepared catalysts on a carrier are loaded in reactor vessels arranged in parallel, so that the reactions to be performed with the catalysts can be done simultaneously. Preferably, after feeding of the reactants, which is preferably performed in parallel in the reactor vessels; the reaction conditions, such as reaction time, temperature and pressure are identical for the catalysts to be tested. This way, the reactions are performed at identical conditions, so that relevant selections of active catalysts can be made. Once selected, the said catalyst can be further tested at reaction conditions that differ from the first selection process to identify one or more catalysts that are optimally suitable for the envisaged reaction conditions. Further, the selection method, that is preferably performed in a gaseous phase in flow mode, can be extrapolated to batch mode reaction for industrial processes for the preparation of amines at suitably mild reaction conditions.

Please amend the section description for the claims on the top of page 13, as follows:

WHAT IS CLAIMED IS: C L A I M S